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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/745,644	12/22/2000	Arnaud Debin	759-13 CON	4038

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EXAMINER
SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
1635	13

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/745,644	Kravtzoff
Examiner	**Art Unit**
Richard Schnizer	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 4, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above, claim(s) *20-30* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-19* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Dec 22, 2000* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *4,5*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

An amendment was received and entered as Paper No. 12 on 4/4/03. Applicant's election without traverse of group 1, claims 1-19 is acknowledged. Claims 20-30 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-19 are under consideration in this Office Action.

Information Disclosure statements were received and entered as Paper Nos. 4 and 5 on 3/29/01 and 4/19/01.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 5-8, 10-14, and 16-19 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 14-17, 24-26, 29, and 30 of U.S. Patent No. 6,214,621 ('621). Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

'621 teaches compositions comprising ionic conjugates comprising oligonucleotides and cationic oligo- or polysaccharides. See claim 1. In one embodiment the oligo- or polysaccharide has a charge in the range of 0.6-1.8 mEq/g. See e.g. claims 2-4. The oligonucleotides may be single or double stranded and may be natural or modified. See e.g. claim 15, and the specification at column 1, lines 15-20. The cationic moiety may be a glycidyl trimethylammonium. See column 9, lines 52-55. The cationic polysaccharide may be 10 kD (Glucidex 6) or 3 kD (Glucidex 6). See e.g. Table III at column 12. The size of the complexes may be between 10 nm and 5 microns, and particularly about 100 nm. See column 6, lines 30-35, and column 14, line 18. Claim 26 teaches a process of making the claimed products in which 0.02 g of oligonucleotide, per hour, is added to a solution of 1 gram of cationic poly- or oligosaccharide. Thus, in the first hour the solution comprises complexes with fewer negative charges than positive charges, i.e. a positive surface charge as required by instant claims 16 and 17, as well as an excess of unbound

cationic poly- or oligosaccharides, as required by instant claim 17. This process also renders obvious instant claims 18 and 19, inasmuch as protection is inherent as a result of making the composition. It is noted that this rejection depends in part upon the teachings of the specification of '624 to teach limitations which are not explicitly recited in its claims. However, while the specification of an issued patent generally cannot be used as prior art to support a double patenting rejection, the courts have found that the portion of a patent disclosure which supports the patent claim may be considered when determining double patenting. "[T]his use of the disclosure is not in contrainvention of the cases forbidding its use as prior art, nor is it applying a patent as a reference under 35 USC 103, since only the disclosure of the invention claimed in the patent may be considered." See In re Vogel 422 F.2d 438, 441-42, 164 USPQ 619 (CCPA 1970), and MPEP 804 (II)(B)(1). In this case the disclosure of '624 explicitly describes the nature of the oligonucleotides recited in the claims, providing support for double stranded oligos. The disclosure also describes the types of cationic moieties that claims 26-30 require to render the oligo and polysaccharides cationic, exemplifies molecular weights and sizes of the claimed cationic polysaccharides. Thus the specification is only relied upon to determine the nature of what is embraced by the claims.

Claim 15 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 14-17, 24-26, 29, and 30 of U.S. Patent No. 6,214,621 ('621), as applied to instant claims 1-3, 5-8, 10-14, and 16-19 above, and further in

view of Rolland et al (US Patent 6,251,599, issued 6/26/01) and Szoka et al (US Patent 5,972,600 issued 10/26/1999).

The teachings of '621 are summarized above. '621 does not teach a cationized polyhydroxylated molecule/nucleic acid complex with a charge ratio of 0.3 to 1 wherein the complex is globally negative.

Rolland teaches that the charge ratios of complexes of nucleic acids and the cationic polyhydroxylated compound chitosan can be adjusted by varying the ratio of nucleic acid to chitosan. Generally, the value of the surface charge increases with the concentration of chitosan. See column 29, lines 18-22.. See also *e.g.* Figs. 7, which shows that a complex having a charge ratio of 0.8 (+/-) has a negative surface charge.

Szoka teaches that while positively charged DNA delivery complexes are preferred under certain circumstances, negatively charged DNA delivery complexes are preferred under others, such as transfection in media containing high serum concentrations. See column 7, lines 33-41.

It would have been obvious to one of ordinary skill in the art at the time of the invention to add to the cationized polyhydroxylated molecules of '621 sufficient nucleic acid to result in a globally negatively charged complex. One would have been motivated to do so because Szoka teaches that negatively charged DNA delivery complexes have advantages under certain circumstances, such as in media with high serum concentrations. One could have done so with a reasonable expectation of success because Rolland teaches that one can produce a globally

negatively charged complex by adjusting the ratio of nucleic acid to cationic polyhydroxylated compound in a complex.

Claims 1-8, 10, 12-14, and 18 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8, 15, 16, 21, 36-40, and 43-48 of U.S. Patent No. 6,017,513 ('513). Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

'513 teaches compositions comprising ionic conjugates comprising RNA or DNA and cationic oligo- or polysaccharides. See e.g. claims 1-5, 36, and 37. In one embodiment the oligo- or polysaccharide has a charge in the range of 0-2 mEq/g. See e.g. claim 4. The RNA or DNA may be in the form of oligonucleotides or expressible (double stranded) polynucleotides. See column 9, lines 44-51. The cationic moiety may be a primary, secondary, tertiary or quaternary amine. See claim 6. The cationic polysaccharide may be 3-10 kD. See column 5, lines 35-39. The size of the complexes may be between 20 and 200 nm. See claim 15. Claims 39 and 40 teach methods of delivering in vivo a complex comprising the instantly claimed invention. These methods render obvious a method of protecting a nucleic acid by complexing it with a cationized polyhydroxylated compound, because they implicitly require formation of such a complex. It is noted that this rejection depends in part upon the teachings of the specification of '513 to teach limitations which are not explicitly recited in its claims. However, while the specification of an issued patent generally cannot be used as prior art to support a double patenting rejection, the

courts have found that the portion of a patent disclosure which supports the patent claim may be considered when determining double patenting. "[T]his use of the disclosure is not in contrainvention of the cases forbidding its use as prior art, nor is it applying a patent as a reference under 35 USC 103, since only the disclosure of the invention claimed in the patent may be considered." See In re Vogel 422 F.2d 438, 441-42, 164 USPQ 619 (CCPA 1970), and MPEP 804 (II)(B)(1). In this case the disclosure of '513 explicitly describes the nature of the nucleic acids recited in the claims, providing support for oligonucleotides and double and single stranded polynucleotides, and describes the nature of the polysaccharides and oligosaccharides, providing support for particular molecular weight ranges. Thus the specification is only relied upon to determine the nature of what is embraced by the claims.

Claim Rejections - 35 USC § 112

Claims 1-11 and 14-19 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for complexes comprising cationized polyhydroxylated molecules with a charge up to 1 mEq/g, wherein the molecule is not a monosaccharide, does not reasonably provide enablement for cationized monosaccharides with a charge of 1 mEq or less. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 1-11 and 14-19 embrace an embodiment in which a biodegradable cationized polyhydroxylated molecule has a charge up to 1 mEq/g and is a monosaccharide. Claim 9 is

specifically limited to this embodiment. In order for a single molecule to be cationic and to have a charge less than 1 mEq/g, the molecule must have a molecular weight of greater than 1000 g/mole. Neither the specification nor the prior art of record teaches a monosaccharide with a molecular weight of greater than 1000 g/mole. While Applicant is not required to disclose that which is well known in the art, there is an obligation to disclose critical elements of the invention as well as how to use these elements. In Genentech, Inc, v Novo Nordisk A/S, the court found that when the specification omits any specific starting material required to practice an invention, or the conditions under which a process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, the identification of monosaccharide with a molecular weight of greater than 1000 g/mole cannot be considered a minor detail which can be omitted in the process of providing an enabling disclosure, and one of skill in the art would have to perform undue experimentation in order to either discover or create a monosaccharide with a molecular weight of greater than 1000 g/mole.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-16 and 19 are indefinite because it is unclear to which particulate complex they refer. Substitution of the definite article "the" for the indefinite article "A" is suggested.

Claims 3 and 4 are indefinite because it is unclear what are the metes and bounds of "natural" and "chemically modified". Specifically, it is not clear if a synthetic oligonucleotide or polynucleotide that is structurally identical to a natural synthetic oligonucleotide or polynucleotide would be considered to be synthetic or natural, thus one cannot know what oligonucleotides and polynucleotides are embraced by the claims. Further, all oligonucleotides and polynucleotides could be considered to be chemically modified merely by the addition of nucleobases during synthesis. Because Applicant does not define "chemically modified" it is unclear as to whether this scope is intended to be embraced by the claims, and one of skill in the art cannot know what are the metes and bounds of the protection sought by Applicant.

Claim 14 is indefinite because it requires a particle of approximately 100 nm to 1 micron, but fails to recite what dimension must have this measurement. Thus one of skill in the art cannot know if Applicant intends to limit the measurement to, for example, radius, diameter, or length.

Claims 15-17 are indefinite because it is unclear to what range of charge ratios they refer. Claim 15 requires a charge ratio of "between approximately 1 to approximately 20". It is suggested that the word "and" should be substituted for the word "to" in this phrase. A similar amendment is suggested for claim 16.

Claims 18 and 19 are indefinite because the method steps are not concordant with the purpose set froth in the preamble. The method recites no step in which protection is achieved. Further, these claims are indefinite because it is unclear from what the nucleic acid is being protected, so it is unclear what scope of protecting applicant intends the claim to encompass. Does "protecting" embrace protection from entering certain cellular compartments such as endosomes? Does it mean protection from sequestration in the cytoplasm as opposed to delivery to the nucleus? Does it mean protection from methylation in the nucleus? It is recommended that the claim should be amended to recite "protecting from nucleolytic degradation" as this scope is supported at page 9, lines 7-9.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-8, 10, 12-14, and 18 are rejected under 35 U.S.C. 102(a) as being anticipated by Betbeder et al (US Patent 6,017,513, issued 1/25/2000) .

Betbeder teaches compositions comprising ionic conjugates comprising RNA or DNA and cationic oligo- or polysaccharides. See e.g. claims 1-5, 36, and 37. The oligo- or polysaccharide can have a charge of 0.2, 0.4, 0.6, or 0.8 mEq/g. See column 5, lines 35-39. The RNA or DNA may be in the form of oligonucleotides or expressible (double stranded) polynucleotides. See column 9, lines 44-51. The cationic moiety may be a primary, secondary, tertiary or quaternary amine. See claim 6. The cationic polysaccharide may be 3-10 kD. See column 5, lines 35-39. The size of the complexes may be between 20 and 200 nm. See claim 15. Claims 39 and 40 teach methods of delivering in vivo a complex comprising the instantly claimed invention. These methods anticipate a method of protecting a nucleic acid by complexing it with a cationized polyhydroxylated compound, because they implicitly require formation of such a complex.

Thus Betbeder anticipates the claims.

Claims 1-8, 10, 12-14, and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Betbeder et al (WO 98/29099, published 7/9/98).

Betbeder teaches compositions comprising ionic conjugates comprising RNA or DNA and cationic oligo- or polysaccharides. See e.g. claims 1-6, 36, and 37. In one embodiment the oligo- or polysaccharide has a charge of 0.2, 0.4, 0.6, or 0.8 mEq/g. See e.g. claim 4, and page 9, lines 7-10. The RNA or DNA may be in the form of oligonucleotides or expressible polynucleotides.

See page 15, lines 22-25. The cationic moiety may be a primary, secondary, tertiary or quaternary amine. See claim 6. The cationic polysaccharide may be 3-10 kD. See page 8, lines 17-19. The size of the complexes may be between 20 and 200 nm. See claim 15. Claims 39 and 40 teach methods of delivering in vivo a complex comprising the instantly claimed invention. These methods anticipate a method of protecting a nucleic acid by complexing it with a cationized polyhydroxylated compound, because they implicitly require formation of such a complex.

Thus Betbeder anticipates the claims.

Claims 1-3, 5-8, 10-14, and 16-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Betbeder et al (WO 98/29557, published 7/9/98) .

Betbeder teaches compositions comprising ionic conjugates comprising oligonucleotides and cationic oligo- or polysaccharides. See claim 1. In one embodiment the oligo- or polysaccharide has a charge in the range of 0.6-1.8 mEq/g. See e.g. claims 3 and 4. The oligonucleotides may be single or double stranded and may be natural or modified. See e.g. claim 14, and the specification at 1 lines 10-29. The cationic moiety may be a glycidyl trimethylammonium. See page 19, lines 30-32. The cationic polysaccharide may be 10 kD (Glucidex 6) or 3 kD (Glucidex 6). See e.g. Table III at pages 25 and 26. The size of the complexes may be between 10 nm and 5 microns, and particularly about 100 nm. See paragraph bridging pages 9 and 10 and Table V at page 29. Claim 27 teaches a process of making the claimed products in which 0.02 g of oligonucleotide, per hour, is added to a solution of 1 gram of

cationic poly- or oligosaccharide. Thus, in the first hour the solution comprises complexes with fewer negative charges than positive charges, i.e. a positive surface charge as required by instant claims 16 and 17, as well as an excess of unbound cationic poly- or oligosaccharides, as required by instant claim 17. This process also anticipates instant claims 18 and 19, inasmuch as the required protection is inherent as a result of making the composition.

Thus Betbeder anticipates the claims.

The following is a quotation of the appropriate paragraph of 35 U.S.C. § 102 in view of the AIPA and H.R. 2215 that forms the basis for following two rejections:

> A person shall be entitled to a patent unless -
>
> > (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-8, 10, 12-14, and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Betbeder et al (US Patent 6,017,513, issued 1/25/2000) .

Betbeder teaches compositions comprising ionic conjugates comprising RNA or DNA and cationic oligo- or polysaccharides. See e.g. claims 1-5, 36, and 37. The oligo- or polysaccharide can have a charge of 0.2, 0.4, 0.6, or 0.8 mEq/g. See column 5, lines 35-39. The RNA or DNA may be in the form of oligonucleotides or expressible (double

stranded) polynucleotides. See column 9, lines 44-51. The cationic moiety may be a primary, secondary, tertiary or quaternary amine. See claim 6. The cationic polysaccharide may be 3-10 kD. See column 5, lines 35-39. The size of the complexes may be between 20 and 200 nm. See claim 15. Claims 39 and 40 teach methods of delivering in vivo a complex comprising the instantly claimed invention. These methods anticipate instant claims 18 and 19, inasmuch as the required protection is inherent as a result of making the composition.

Thus Betbeder anticipates the claims.

Claims 1-8, 10, 12-14, and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Betbeder et al (US Patent 6,096,291, issued 8/1/2000) .

Betbeder teaches compositions comprising ionic conjugates comprising RNA or DNA and cationic oligo- or polysaccharides. See e.g. abstract; column 4, lines 25-67. The oligo- or polysaccharide can have a charge of 0.2, 0.4, 0.6, or 0.8 mEq/g. See column 5, lines 22-26. The RNA or DNA may be in the form of oligonucleotides or expressible (double stranded) polynucleotides. See column 9, lines 4-11. The cationic moiety may be a primary, secondary, tertiary or quaternary amine. See column 5, lines 41-56. The cationic polysaccharide may be 3-10 kD. See column 4, lines 58-67. The size of the complexes may be between 20 and 200 nm. See column 7, lines 1-10. The nucleic acid may be located at the outer surface of the polysaccharide or oligosaccharide, or located in

the inner core of the polysaccharide or oligosaccharide. This would inherently result in protection of the nucleic acid from nucleases as the polysaccharide or oligosaccharide would cause steric hindrance, particularly in the situation in which the nucleic acid was sequestered within the core of a cross-linked polysaccharide or oligosaccharide.

Thus Betbeder anticipates the claims.

The following is a quotation of the appropriate paragraph of 35 U.S.C. § 102 prior to the amendment by the AIPA that forms the basis for the rejection that follows:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-3, 5-8, 10-14, and 16-19 are rejected under 35 U.S.C. 102(e) as being anticipated by Betbeder et al (US Patent 6,214,621, issued 4/10/01, claiming priority to PCT/FR97/02332, filed 12/27/97).

Betbeder teaches compositions comprising ionic conjugates comprising oligonucleotides and cationic oligo- or polysaccharides. See claim 1. In one embodiment the oligo- or polysaccharide has a charge in the range of 0.6-1.8 mEq/g. See e.g. claims 2-4. The oligonucleotides may be single or double stranded and may be natural or modified. See e.g. claim 15, and the specification at column 1, lines 15-20. The cationic moiety may be a glycidyl trimethylammonium. See column 9, lines 52-55. The cationic

polysaccharide may be 10 kD (Glucidex 6) or 3 kD (Glucidex 6). See e.g. Table III at column 12. The size of the complexes may be between 10 nm and 5 microns, and particularly about 100 nm. See column 6, lines 30-35, and column 14, line 18. Claim 26 teaches a process of making the claimed products in which 0.02 g of oligonucleotide, per hour, is added to a solution of 1 gram of cationic poly- or oligosaccharide. Thus, in the first hour the solution comprises complexes with fewer negative charges than positive charges, i.e. a positive surface charge as required by instant claims 16 and 17, as well as an excess of unbound cationic poly- or oligosaccharides, as required by instant claim 17. This process also anticipates instant claims 18 and 19, inasmuch as protection is inherent as a result of making the composition.

Thus Betbeder anticipates the claims.

It is noted that this patent is the priority document to which US 6,214,621 to Betbeder claims priority as a national stage application. For this reason US 6,214,621, cited above, is considered to be an English language equivalent of this French document.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Betbeder et al (US Patent 6,214,621, issued 4/10/01) in view of Rolland et al (US Patent 6,251,599, issued 6/26/01) and Szoka et al (US Patent 5,972,600 issued 10/26/1999).

Betbeder teaches compositions comprising ionic conjugates comprising oligonucleotides and cationic oligo- or polysaccharides. See claim 1. In one embodiment the oligo- or polysaccharide has a charge in the range of 0.6-1.8 mEq/g. See e.g. claims 2-4. The oligonucleotides may be single or double stranded and may be natural or modified. See e.g. claim 15, and the specification at column 1, lines 15-20. The cationic moiety may be a glycidyl trimethylammonium. See column 9, lines 52-55. The cationic polysaccharide may be 10 kD (Glucidex 6) or 3 kD (Glucidex 6). See e.g. Table III at column 12. The size of the complexes may be between 10 nm and 5 microns, and particularly about 100 nm. See column 6, lines 30-35, and column 14, line 18. Claim 26 teaches a process of making the claimed products in which 0.02 g of oligonucleotide, per hour, is added to a solution of 1 gram of cationic poly- or oligosaccharide. Thus, in the first hour the solution comprises complexes with fewer negative charges than positive charges, i.e. a positive surface charge as required by instant claims 16 and 17, as well as an excess of unbound cationic poly- or oligosaccharides, as required by instant claim 17. This process also renders obvious instant claims 18 and 19, inasmuch as protection is inherent as a result of making the composition.

Betbeder does not teach a cationized polyhydroxylated molecule/nucleic acid complex with a charge ratio of 0.3 to 1 wherein the complex is globally negative.

Rolland teaches that the charge ratios of complexes of nucleic acids and the cationic polyhydroxylated compound chitosan can be adjusted by varying the ratio of nucleic acid to chitosan. Generally, the value of the surface charge increases with the concentration of chitosan. See column 29, lines 18-22.. See also *e.g.* Figs. 7, which shows that a complex having a charge ratio of 0.8 (+/-) has a negative surface charge.

Szoka teaches that while positively charged DNA delivery complexes are preferred under certain circumstances, negatively charged DNA delivery complexes are preferred under others, such as transfection in media containing high serum concentrations. See column 7, lines 33-41.

It would have been obvious to one of ordinary skill in the art at the time of the invention to add to the cationized polyhydroxylated molecules of '621 sufficient nucleic acid to result in a globally negatively charged complex. One would have been motivated to do so because Szoka teaches that negatively charged DNA delivery complexes have advantages under certain circumstances, such as in media with high serum concentrations. One could have done so with a reasonable expectation of success because Rolland teaches that one can produce a globally negatively charged complex by adjusting the ratio of nucleic acid to cationic polyhydroxylated compound in a complex.

Thus the invention as a whole was prima facie obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.